Drug Utilization Study in Dengue Infection in A Tertiary Care Hospital in Bangladesh

By

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A project submitted to the Department of Pharmacy in partial fulfillment of the
requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at BRAC University.

2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

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Approval

The project titled "Drug utilization study in dengue infection in a tertiary care hospital in Bangladesh" submitted by Sudipto kundu (16146048) of Spring 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 27 February, 2020.

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Ethics Statement

This study is free from any kind of human or animal trial.

Abstract

Dengue virus contamination has become a significant global health concern in present era. Drugs prescribing indicators, facility indicators, patients care indicators and complimentary indicators were analyzed throughout this research. A total 60 prescriptions were analyzed. The ratio of men and female patients was 41:19 and the most affected age group belongs to 40-49 years old (15 patients). Most commonly prescribed drugs were antipyretics, antacid, antiemetic and multivitamin. The consultation time was 4-5 minutes per patients. The hospital pharmacy kept all the key drugs and also had the copy of essential drug list. Antibiotic was prescribed in some prescriptions though it is prohibited in the national guideline. Anti-pyretic and antiemetic were common in all prescriptions. Finally, along with the government all people should come forward to take preventive steps to control dengue virus and its prevalence.

Keywords

Dedication

This work is dedicated to my lovable parents for their love, motivation and constant support

Acknowledgement

All praise belongs to the Almighty God for giving me the strength, patience, and good health to complete my project work and the courses necessary to complete Bachelor of Pharmacy (Hons.) program.

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List of Acronyms

WHO	World Health Organization
DSS	Dengue Shock Syndrome
DHF	Dengue Hemorrhage Fever
DENV	Dengue Virus
SD	Several Dengue
DF	Dengue Fever
EC	Endothelial Cell
IgG	Immunoglobulin G
NS 1	Nonstructural protein 1
EIP	Extrinsic incubation period
ORS	Oral rehydration salt
NTD	Neglected Tropical Diseases
ELISA	Enzyme-linked immunosorbent assay
RT-PCR	Reverse transcription polymerase chain reaction
PCR	Polymerase chain reaction
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAF	Platelet-activating factor

Chapter 1

Introduction

1.1 Background

Dengue is one of the most common rapidly spreading arthropod-borne viral diseases of many tropic and subtropics regions that can occur epidemically. Dengue fever is caused by dengue virus (Abbasi, 2017). In developing countries like Bangladesh dengue causes mortality, morbidity and high economic cost to the population (Harapan et al., 2018). The World Health Organization (WHO) has marked about 20% of world's population which is around 3.6 billion people is at risk of dengue fever. Currently more than 125 countries has reached in an epidemic form of dengue (Kumar & Mansoor, 2015)-(Sam, Omar, Teoh, Abd-Jamil, & AbuBakar, 2013). Some factors like climate change, trade and travels, globalization, viral evolution, urbanization, socioeconomic status, ecological disturbance etc. are responsible for the rapid explanation of dengue virus (Ajibola, Shohaimi, Adam, Nadzir, & Segun, 2018). Dengue virus has a microscopic structure which can replicate in the host for survival and growth (Grard et al., 2007). It is transmitted by the bite of female mosquitoes mainly of the species *Aedes aegypti* and *Aedes Albopictus. Aedes aegypti* is also called "tiger mosquito" and the other species normally found in urban areas (Goel, Patel, Lakhani, Agarwal, & Agarwal, 2004). Dengue virus belongs to the family of Flaviviridae and in the genus of Flavivirus with positive polarity (Mishra, Agrahari, & Shah, 2017). Flavivirus generally includes yellow fever, tick-borne encephalitis virus, west Nile, and Japanese encephalitis (Dey & Mukhopadhyay, 2017). There are four types of serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) of dengue virus and all can cause a wide spectrum of disease. Infection caused by one dengue virus serotype normally results in a long-term immunity to the same viral serotype.

That means dengue fever caused by one serotype provides immunity of the same serotype but there is a risk of affecting by other viral serotypes that may cause dengue fever which is very fatal (Warkentien, 2016). Recently a new serotype has been invented which the latest addition is called DENV-5. DENV-5 has been found in Malaysia while screening of viral blood sample from a farmer aged 37 and full genetic sequences was found of this fifth serotype. It is four times stronger than the other serotypes (Mustafa, Rasotgi, Jain, & Gupta, 2015). The transmission cycle of dengue virus is "Man-Mosquito-Man". Mosquito and human both are reservoir of dengue virus (Montoya, Loaiza, & Tost, 2016). The female mosquito mainly transmit virus to the human as it needs blood to get protein for laying eggs. The incubation period is 4-10 days and after that the infected mosquito is ready to transmit virus to the host and it continues for its entire life (Zameer, Ashraf, Mukhtar, & Ahmad, 2013). The symptoms of dengue infection are high fever, painful joints, severe headache and muscles, nausea, aches, vomiting, pain behind the eyes, during movement of eyes and skin rashes. Normally these symptoms continue one week but tiredness and weakness may remain couple of weeks. Actually signs symptoms vary according to the severity of the disease (World Health Organisation-South-East Asian Regional Office, 2019). According to WHO three types of severity was established as DF (Dengue fever) without warning sign, DF without warning sign and severe dengue (SD). Severe dengue is life threating because it causes severe plasma leakage, such as pleural effusion, damage in organ like liver, heart and central nervous system, sever bleeding. The most severe form of dengue fever is dengue hemorrhage fever (DHF) which is connected with dengue shock syndrome (DSS). All people may acquire DHF but children under age of 15 are more susceptible to it. It may turn from self-limiting to life- threating if proper treatment is not taken and most of the case fatality may exceed 25% (Vazhayil, Stephen, & Kumar, 2017)

1.2 Aim of the study

The principal aim of this research was to verify the use of proper drugs and the treatment strategy among the dengue patients in hospital settings in Bangladesh. To evaluate if the proper drugs were being prescribed or not and how much positive or negative impact the patients were facing term of drug safety, efficacy, duration and economic aspects in all stage of the disease. Throughout this research the treatment criteria and the percentage of different ages of patients was analyzed. This study also focused on prescribing indicators, patient care indicators, facility indicator and complimentary indicators in aspect of dengue patients. It will assist in contributing to rational use of drugs in more practical way.

1.3 Significance of the study

In the present decade dengue has become one the most life threating and communicable disease in the world. In Bangladesh's perspective the people are also at risk of it. Our treatment strategy and patient counselling need to be improved. For this, along with treatment, patients care indicators are also important to tackle the virus. Patients safety and drug efficacy should be maintained carefully. Through this survey our treatment gaps were identified for better treatment in the future. People of all ages and gender has different immunity and thus treatment varied person to person and it was highlighted in this study. Drug list, category of drugs, use of generic or brand medicine and patients care processes in the hospitals were explained throughout the study. This survey hopefully helped to find out our strength or weakness in all sectors of dengue management.

Chapter 2

Literature Review

2.1 Epidemiology

The expansion of the dengue fever was 30-fold in past 50 years throughout the world and by passes of time the virus is spreading quickly. That means the propagation of geographical areas as well as new region has been increased. In today's decade the rural areas are also at risk beside urban area. The amount of affected people is nearly 2.5 billion in dengue epidemic countries (Istúriz, Gubler, & Brea del Castillo, 2000) . Approximately 75 percent of dengue affected people live in Asia and Pacific region and 70 percent of civilization is in danger of dengue virus (Ramos et al., 2008). Bangladesh, Maldives, India, Sri Lanka, Myanmar, Indonesia, Thailand and Timor-Leste have already reported about the virus in 2003. In 2004 Bhutan and in 2006 Nepal has reported their first dengue cases (*R e s o l u t i o n*, 2008). However, the percentage has increased rapidly. In tropical monsoon, the progress of spreading dengue virus is much more serious in rainy season (Assembly, 2002)-(Rahman & Breiman, 2011). Lack of reporting dengue virus is a common problem in all regions because physicians and researchers cannot find a good solution if all data are not given to them. In Bangladesh the number of dengue patients has been doubled now in comparison of last 19 years (Islam, Region, Region, Lanka, & Alert, 2019). There are many factors which influence how the dengue virus spreads and becomes an epidemic. The factors are: -

   i.   The risen virulence of virus subtype or serotype

  ii.   Population's less knowledge about the genetics and viral genome,

 iii.   In condition of micro climate there is less data or evidence about viral ecology, natural immunity of the viral affected patients and the spread of infections,

iv.   Time gap of contagious process and son on (Islam et al., 2019).

World health organization (WHO) has presented a data mentioning that in a year 50-100 million people are being suffered by dengue infection. And among them 5 lakhs of people suffer from dengue hemorrhage fever which in turns causes death of 22 thousand of people. To add, among the died people maximum number of them were children (Sanyaolu, 2017).

If we consider the past, dengue is dominating for centuries. The very first symptom of the dengue virus was established in 992 AD (Anno Domini) in the Chinese medical encyclopedia (Press, 2015). At first the disease was known as Water Poison and it was predicted that flying related insects are the cause of spreading the virus. In 1780 an epidemic happened in Philadelphia (Press, 2015). After that throughout the United States the virus stared to progress. On outbreak occurred in 1945 in the New Orleans. The origin of the vector which is mainly *Aedes aegypti* was from either Asia or Africa. Mainly over the previous five to six decades dengue has spread epidemically and thousands of dengue reports has established. At present, dengue virus has spread worldwide. About three-fourth of the people live in the Asia-pacific region. In this region, hospitalization and death occurs much among the population and the number is increasing surprisingly. However, an about 187 thousand dengue report was found to WHO here in 2010 (Press, 2015). All types of dengue subtypes are present in South east Asia. The severity is 18 times strong in Southeast Asia than America. In western pacific in the year of 2010 about 353 thousand dengue repots was found. Among them one thousand people died. About nine out of ten reports in Pacific was found from French Polynesia, Australia, New Caledonia and Vanuatu (Press, 2015). However, in 1964 dengue serotype 3 was introduced in Pacific Island from America. In the gap of 25 years, the fourth serotype also entered in the Pacific region. Gradually, the all four serotypes spread out all over this region. In Northern Queensland, which is in Australia faced dengue outbreak in 2019 and 2010

where about one thousand people died (Press, 2015)-(Arima, Matsui, Polynesia, Caledonia, & Nam, 2011). In America, the epidemic form of dengue virus is almost the same of the southeast Asia where all types of serotypes exist. In 2010 about 1.6 million dengue reports were found in America where 50 thousand was serious cases. In Latin America all countries are bearing the virus except Continental chile and Uruguay (Press, 2015)-(Luis et al., 2010). In the European region dengue was epidemic about 90 years ago. In Greece then the frequency was very severe and the mortality rate was very high. Here the vector was *Aedes aegypti.* A surprising incident is that there was no dengue infection around 60 to 65 years in the region. When another species *Aedes albopictus* was strong then again, the dengue virus started to attract. As foreigner also carry the virus, thus why right now all over the county the virus is dominating (Press, 2015)-(*Treatment, prevention and control global strategy for dengue prevention and control 2*, n.d.). However, according to expert's dengue will cause severe problem in the future as the virulence is increasing and the transmission is also frequent. In non-human primate the virus is also spreading and that is neither prevented nor treated. So, there is a chance of attacking new serotypes which would be more life threating (Press, 2015)

2.2 Pathogenesis

The major impact of dengue infection occurs due to the cell and tissue tropism of the dengue virus. The role of dengue virus tropism is quietly hard to understand because of the presence of animal disease model. However, there are three organ methods which are mainly responsible in the pathogenesis of dengue virus according to autopsy studies and in vitro data. They are the immune

system, (EC) endothelial cell linings of blood vessels and the liver (Martina, Koraka, & Osterhaus, 2009).

i. **Cells of immune system:** When the mosquito bites, the virus enters into the bloodstream of the host which spillover the dermis and epidermis. As a result, infection occurs in the immature Langerhans cells which is mainly epidermal dendritic cells and also in keratinocytes (U et al., 2000)-(Limon-flores et al., 2005). Noticeably, from their site of infection the infected cells after that migrates to lymph nodes. Here, the target of infection is monocytes and macrophages (Durbin et al., 2008). Dengue virus has been exhibited to have the tropism to circulate mononuclear cells in blood and for cells residing in the lymph nodes, spleen, bone marrow of infected AGT129 infected mice (Meier, Gardner, Khoretonenko, Klimstra, & Ryman, 2009). In non-human animals' dengue virus is able to infect the leukocytes (Zompi & Harris, 2012). Another important part is that the mononuclear cells absorb the DENV-specific immunoglobulin G (IgG) during the secondary infections adjacent to heterologous dengue virus. As a result the mononuclear cell die by apoptosis (Torrentes-carvalho et al., 2009)-(Rodriguez-madoz, Bernal-rubio, Kaminski, Boyd, & Fernandez-sesma, 2010). Additionally the bone marrow is susceptible to infection due to dengue virus (Rodriguez-madoz et al., 2010)-(Manuscript, 2013)-(Suzuki, Winkelmann, & Mason, 2009).

ii. **Organ pathology:** Thousands of patients had been identified dengue in last 60 years in Southeast Asia and America. Only a few patients were being performed autopsy. So, the acute phase was not clear. Histopathological investigation is hard because the fatal causes of DSS and DHF are very rare and another cause is lack of laboratory technology in the

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rural area where it occurs more. Again, due to religious belief and culture autopsy it is not possible for many fatal causes. A review was done from the 160-autopsy sample of fatal cases among them most of the sample belongs to children between 4-18 years old (Martina et al., 2009). Dengue virus cell tropism was identified from the perusal of in situ hybridization, polymerase chain reaction and virus isolation technique and immunohistochemistry. In some cases who died the in between 36 hours of shock syndrome , the existence of dengue virus is in skin (Martina et al., 2009), spleen, thymus (Chitkara, Chhina, Gupta, Mahajan, & Sharma, 2018), bone marrow (Halstead & Cohen, 2015), lung, brain (Jan, Chen, Ma, Liu, & Tsai, 2000), liver and lymph node (Aguiar, 2005)-(Balsitis et al., 2009). Virus can be isolated from the peripheral blood, mononuclear cells and liver. However, from gastrointestinal tract and skin high concentration of virus was isolated. On the other hand, low concentration of dengue virus was found in thymus, spleen and some peripheral lymph nodes (Martina et al., 2009). Dengue virus was recovered from thymus, spleen, lymph nodes and several central nervous of mice (Balsitis et al., 2009). An important part is that while shock sets, in blood the virus was not no longer identified (Libraty et al., 2000). In human and mouse model dengue virus is commonly occurs is liver. They elevate the liver enzyme level and risk of continuous bleeding (Soundravally, Narayanan, Bhat, Soundraragavan, & Setia, 2010)-(Barreto, Costa, Oliveira, & Nogueira, 2005). Severe hepatic damage was not found in dengue virus (Wichmann et al., 2007). There was huge amount of dengue virus in the hepatocytes as well as Kupffer cells which causes inflammation. Besides, cell necrosis and apoptosis were induced virally. If the apoptosis is higher than necrosis then the inflammation is less (Quaresma et al., 2007)-(Quaresma et al., 2006).

iii. **Endothelial cell:** The coagulation response upon excessive systemic inflammation, endothelial cell plays a great role. Its integrity is physiologically regulated by so many factors. Dengue virus's tropism for the endothelial cell in vivo is controversial. After researching of some cases, it has been found in skin biopsy that the main site of affected point is microvasculature which is located in the dermal papillae. However, the dengue virus antigen was not detected in the endothelial cell but surrounding the microvasculature dengue virus antigen was detected (Juffrie et al., 2000)-(Kelley, Kaufusi, & Nerurkar, 2012). On the other hand it is observed that the presence of dengue virus antigen in pulmonary vascular endothelium (Rodriguez-madoz et al., 2010). In vitro study has evidence that all dengue virus subtype can replicate in endothelial cell actively and the result of infection is functional , not morphological damage (Huang et al., 2000)-(Dalrymple & Mackow, 2011)-(Yen et al., 2008). The dengue virus infection has different activation pattern in different tissues of endothelial cell. Again, in DSS and DHF there occurs excessive peripheral microvascular permeability. Due to this, selective vascular leakage syndrome is noticed (Bethell et al., 2001)-(Chen, Hofman, Kung, Lin, & Wu-hsieh, 2007) . It has found that the major (NS1) nonstructural protein 1 of dengue virus binds to endothelial cells which in further causes selective pulmonary vascular leakage (Avirutnan, Zhang, Punyadee, Manuyakorn, & Puttikhunt, 2007).
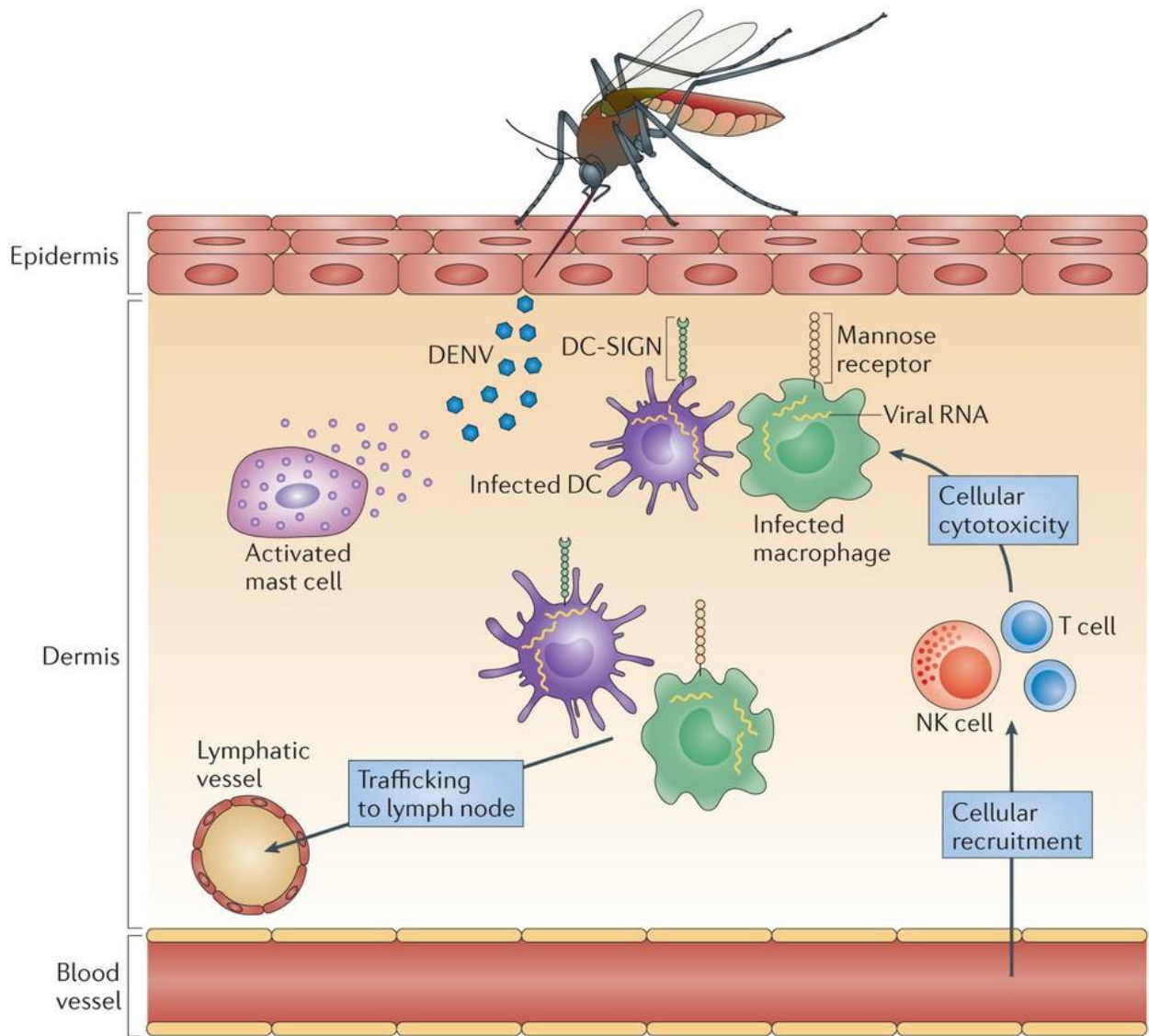
Figure 1: Dengue Pathogenesis. Host responses to cutaneous dengue virus injection (St. John, Abraham, & Gubler, 2013).

2.3 Transmission and life cycle

The transmission of dengue virus occurs in two ways. One is from mosquito to human and another is human to mosquito.

i. **Mosquito-to-human transmission**: When an infected female mosquito bites a health human the virus is transmitted to the human body. Only a few species mosquito are considered as vector for the virus. A vector is considered as vehicles which transmit viruses to the host organisms. Dengue virus does not pass from human to human. it must need a vector. Normally the *Aedes Aegypti* mosquito occurs more viral causes. It also spreads Zika and chikungunya viruses. *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scutellaris* also do harm but not that much strongly (Carrington, Armijos, Lambrechts, & Scott, 2013). Aedes aegypti is dark and small mosquito which can be recognized by white band on legs and silver-white pattern of scales on its full body. It is a day time feeder. The most biting periods are early in the morning and in the evening. It can fly up to 400 meters to lay their eggs looking for water-filled area. This kind of mosquito is found in the tropical and subtropical areas where the winter temperature is less cold than 10°C. They cannot survive in the cold weather. They generally stay in warm weather and passes their life adjacent to human livings (Lambrechts, Paaijmans, Fansiri, Carrington, & Kramer, 2011). However, after biting a human, the virus starts replicating in the mosquito's midgut. Then, it diffuses to the secondary tissues like the salivary glands. The time duration needed from ingesting virus to transmission in the new host is known as EIP (extrinsic incubation period) (Ye et al., 2015). Normally the extrinsic incubation period takes around 8-12 days and the ambient temperature is (25-28) °C (Temperature, Vector, & Dengue, 1987)-(Tjaden, Thomas, Fischer, & Beierkuhnlein, 2013). A number of factors play a role in variations in the extrinsic incubation period. Initial viral concentration, the spread of daily

temperature fluctuations, virus genotype are responsible factors for time needed for mosquitos to transmit virus. If a mosquito gets infectious, it is capable of transmitting the viruses for the rest of its whole life (Anderson & Rico-hesse, 2007).
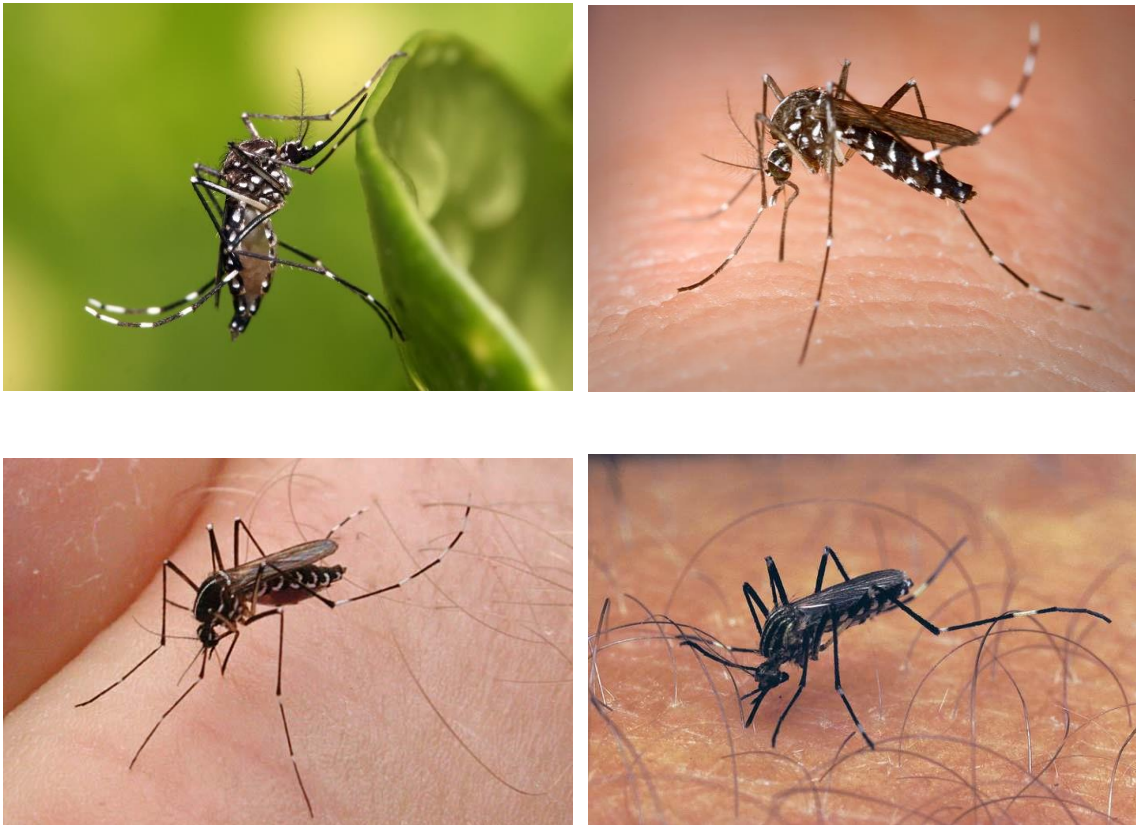
Figure 2,3,4,5: RESPECTIVELY- Aedes Aegypti , Aedes albopictus , Aedes polynesiensis and Aedes scutellaris. [Taken from cdc.gov website]

ii. **Human-to-mosquito transmission:** From human to mosquito dengue viruses can also spread. The person who is carrying the virus is able to transmit it to another human. If the mosquito bites the person the mosquito will also be infected. The person may have symptomatic dengue infection or be pre symptomatic (the person who is yet to show

symptomatic infection). Again, those people who are asymptomatic like no illness or signs can transmit the virus as well (Duong et al., 2015) .From human to mosquito transmission may happen 2 days before the person shows illness and symptoms. Additionally, after 2 days of the recovery of fever the transmission can happen (Gubler, Suharyono, Tan, Abidin, & Sie, 1981)-(Minh et al., 2013).

iii. The normal mode of transmission occurs between human and mosquito but evidence has shown that the virus can transmit from mother to child. The women who are pregnant and affected by the virus may face problems in pregnancy. Besides, the child may suffer from pre-term birth, fetal distress low and low birthweight (Carles, Youssef, & Guindi, n.d.)-(Sinhabahu, Sathananthan, & Malavige, 2014)-(Everhard et al., 2018). Again, children are more suitable to be affected by dengue virus because their immunity is not strong than the adults (Abbasi, 2017).

2.4 Sign and syndrome

When the transmission is done, the virus then starts to attract. One can show some sings and syndrome due to it. Again, some people do not have any sign or a little. About 25% may become sick. Generally high fever occurs. The temperature increases very quickly. Severe headache occurs especially in retro-orbital. Pain in bone and areas around it is felt. Some other signs like rash, myalgia, vomiting, nausea, muscle and joint pain, chest pain, back pain, flushing, anorexia, acute abdominal pain occur (G N Malavige, Fernando, Fernando, & Seneviratne, 2004). The platelet count is decreasing. Along with the platelet, the white blood cells also reduce and leucopenia exits. The affected person will feel weak. Pain also remains in eye (normally behind of eye).

Additionally, bleeding can also take place from nose, wound places (*Nationall_Guideline_Dengue_Syndrome_2013.Pdf*, n.d.). Due to plasma leakage, circulatory disorders occur like narrow pulse pressure, low blood pressure, and tachycardia and so on. Some complication may occur like myocarditis, liver failure, encephalitis, intravascular coagulation (*Nationall_Guideline_Dengue_Syndrome_2013.Pdf*, n.d.).

Headache, fever

Bleeding gums, nose and eyes

Vascular symptoms:
Hypovolaemia
Low blood pressure
Shock

Vascular symptoms:
Leukopenia
Thrombocytopenia
Neutropenia
Late eosinophilia
Reduced coagulation

Hepatic injury
Fluid pooling in
body cavities
Gall bladder
thickening
Haemorrhaging
within organs

Skin symptoms:
Rash
Bruising
Petechiae
Purpura

Vomiting
Intestinal bleeding

Infrequent
complications:
Encephalitis
Acute pancreatitis
Renal failure
Myocarditis
Splenic rupture
Pulmonary haemorrhage

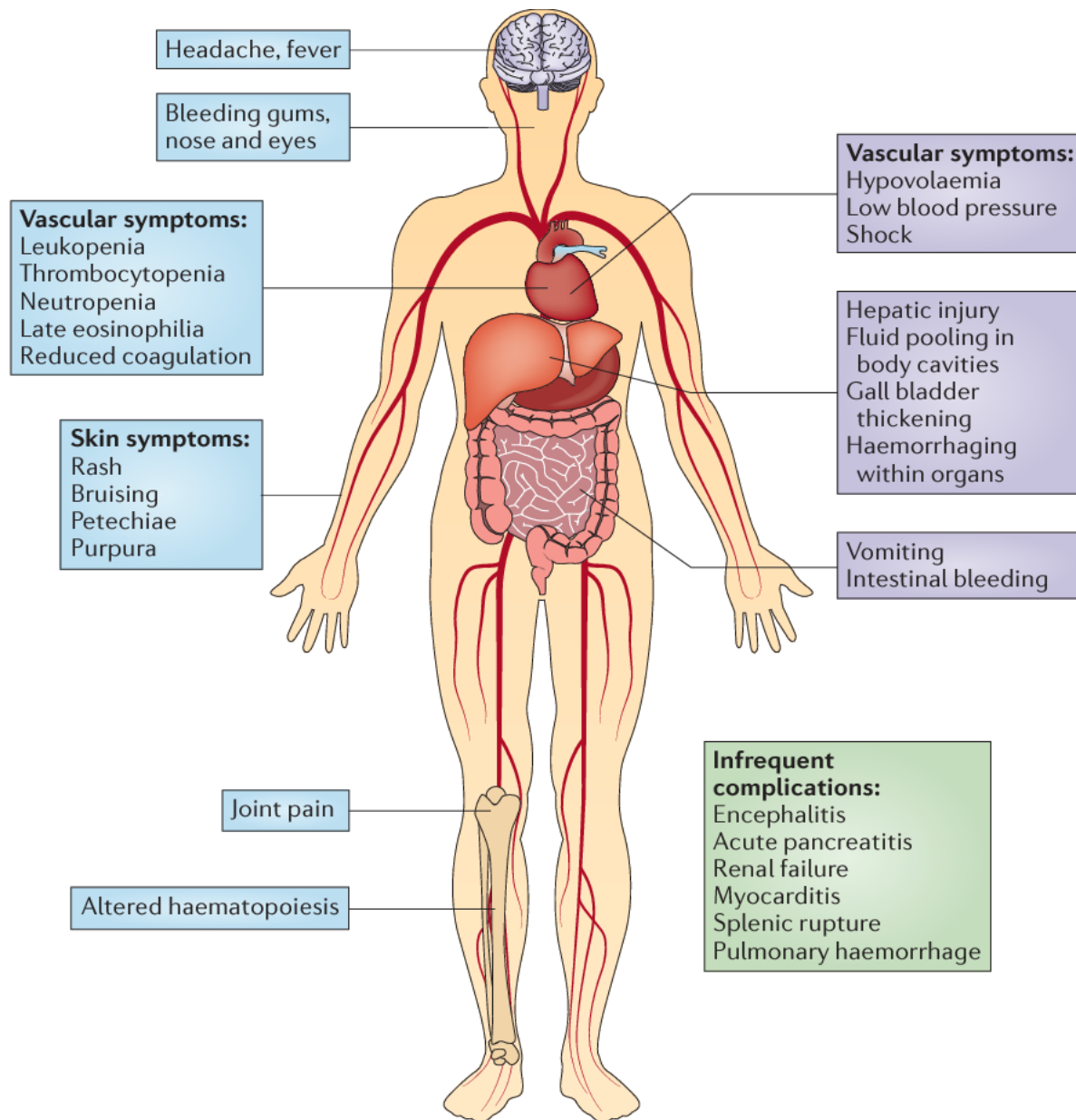Joint pain

Altered haematopoiesis

Figure 6 : Clinical symptoms and pathogenesis of dengue in humans. (St. John et al., 2013)

The most risk factor in dengue fever is dengue hemorrhage fever (DHF) and dengue shock syndrome (DSS). There are four steps of dengue hemorrhage fever. They are DHF (1, 2, 3, 4). In DHF1 fever and hemorrhagic manifestation occurs. There is also a prove of plasma leakage in this stage. In second stage of DHF spontaneous bleeding along with DHF1 are seen. In DHF3 along with both the two categories circulatory failure also seen. In last sector the previous three category occurs with profound shock with undetectable pulse and blood pressure. The DHF3 and DHF4 are called DSS. If shock occurs, there is high risk of death and this is very serious. However, in all stages of DHF and DSS the thrombocytopenia count is $\leq 100000 / mm3$ and hematocrit count is $\geq$ 20% (Asia, Pacific, Mediterranean, & States, 2015)-(*Nationall_Guideline_Dengue_Syndrome_2013.Pdf*, n.d.).

2.5 Treatment

Nowadays, there are no specific drugs for the treatment of dengue disease. People should keep themselves in a mosquito free area or environment. Some factors and treatment system may follow as bellow:

i.   To reduce the temperature and pain antipyretic can be given. Acetaminophen or paracetamol is suitable to decrease the temperature. The dose and frequency of taking antipyretic should be based on the weight and condition of the patients. In children the dose should be lower and around 10mg/kg is generally considered. One thing should keep in mind that medicines like aspirin and other painkillers cannot be given. NASID (nonsteroidal anti-inflammatory drugs) must be avoided. Another important thing is that

use of antibiotics should not be used but in some critical conditions it may be used under the supervision of physicians.

ii. Bed rest is considered while a patient is affected. A huge amount of rest in needed for the patients (Oliver, 2013).

iii. Fluid intake is must for a dengue patient. ORS (oral rehydration salt) can also be given. Again, injectable saline is also needed for patients at that stage when the patient is not able to take orally. Crystalloids (0.9% saline) is considered as the first line fluid for intravenous (Scott, 2009). Half normal saline should not be given because it may cause pleural effusions or ascites.

Use of corticosteroid must be prevented. Water and fluid are recommended to take as much as possible because it will help to prevent fluid loss. It also helps to reduce the body temperature. Solid food should be avoided until the recovery if possible.

iv. The rate of injectable saline should be maintained properly according to the hematocrit concentration level. Hematocrit is needed to count after 4-6 hours. If the patient already takes 1000 ml of fluid by intravenous, he should be in the continuous monitoring. Furthermore, colloidal solution like Dextran 40 is given.

v. In case of thrombocytopenia, and abdominal pain and others syndrome is considered to be hospitalized. They may have shock syndrome. Plasma leakage and loss of blood. So, transfusion needed. The amount should be about 10-20 ml/kg per dose.

vi. For patients who has diabetics require insulin for better result. Again, blood pressure and pulse should measure is a continuous basis.

vii. For treating dengue virus so far there is no official announcement of the use of vaccine. As it a viral disease, so antiviral drugs would work well. In term of vaccine development, a lot

of trail is continuing. Recently, a vaccine type has passed phase III trials named CYD-TDV which is being used to children in Asian countries. Hopefully, a better vaccine would be invented in future for dengue virus (Rajapakse, Rodrigo, & Rajapakse, 2012)-(Oliver, 2013)-(Lewandowski, Co-investigator, & Lewandowski, 2015).

viii. Some herbal and home remedies are also used as treatment from the ancient time. Many natural plants are used for cure. Neem is one of the common ayurvedic plants which is found abundantly in Asian countries and a little in Africa. Leaves and oil of neem is used as purifying agent. Male and female who are seeking a baby should avoid it. Coriander fruit is used to reduce the fever. It is found in the European region. Amla is used to provide vitamin C for better absorption of iron. Holy basil, papaya is also used in the herbal treatment (Singh, Ansari, Ahmad, & Bagga, 2016).

2.6 Prevention

In Neglected Tropical Diseases (NTD) Roadmap dengue is considered one of the 17 NTD in the world. As dengue has no specific treatment and vaccine or drug so far, it the only way to prevent the virus. So, the goal and objective to reduce the dengue epidemic condition is to lower down the morbidity and mortality to 25% and 50% respectively by following 2020 (Madhok, n.d.). Mortality rate can be reduced if proper clinical management is established. Among it includes sufficient laboratory test in proper time, use of oral rehydration salt and use it in intravenous if necessary. Hospital reorganization is also necessary to improve the patient care. Diagnosis is an essential tool in the dengue management system. To identify a patient's current condition different test are necessary because a little delay can harm a lot. Again, in term of emergency condition the treatment

progress result is very crucial. In hospital if the data of every single patient is collected, it will help for the nation. Many researchers are working in prevention of dengue virus but they are not getting enough information for their research. So, hospitals should collaborate with then. In health center others function like tanning and supervision, outbreak investigation, quality assurance must be performed. Moreover, the physicians and nurses should be more conscious and aware of the current situation of the disease and treatment strategy. Surveillance improvement is necessary to report, control and prevention of dengue. Advertisement is also a big factor because the common people do not know much about the disease. They do not know how to tackle this and how to prevent the disease (*Treatment, prevention and control global strategy for dengue prevention and control 2*, n.d.)-(Madhok, n.d.).

Some tests like virus culture, nucleic acid deletion, antigen detection (ELISA) and serology. In virus isolation test the virus must be collected before the disease onset which is known as viremia. From blood, serum, tissues and serum the virus is possible to isolate. As the virus sample is heat sensitive, it can be spoiled by heat. The reservation temperature should in between four to eight degree Celsius. Cell culture is used to observe the virus. All the cell lines of mosquito are not pathogenic. Only few causes in host cell like AP61 or C6/36. They can be identified by screening. Nucleic acid of the virus can be a diagnostic method by detecting the virus. Here, high accuracy is archived in short time. In PCR it can be done and one of the most common technique is RT-PCR. The continuous process is used by maintaining four steps like extraction and purification, amplification, detection and last one is characterization by liquid phase separation. In the process silica kit is used. After the PCR elements are differentiated into electrophoresis gel and put into the UV visible light. Here, the dengue virus serotype is noticed. Some other diagnosis methods are

also used for better identification (Jaweria et al., 2016)-(*Treatment, prevention and control global strategy for dengue prevention and control 2*, n.d.).

As prevention is better than cure, we should be aware of controlling mosquito and its bites. There are many ways to do that. Some points to be noted like: -

i. As eggs of the mosquito especially *Aedes aegypti* can live around 12 months without water, it is very easy to grow in one point by getting a little water. So, we should destroy the area where the mosquito lives and lays eggs. Water is not allowed to remain stagnant around our houses.

ii. Drains must be cleaned properly.

iii. We have to destroy or clean old tires, tin and other containers.

iv. The tray of the fridge and old unused cardboard should be cleaned.

v. Flower vases and sir coolers must be cleaned in between a week.

vi. Plastic bottles, cups, polyethene should be used properly.

vii. Water tanks and pipes, unused cylinder, roof must be cleaned in a regular basis.

viii. Our environment and our surroundings where we belong should keep clean regularly so that the larva or eggs do not get change to develop.

ix. A study has shown that some fish like Gambusia, Lebister fish take mosquito larva as food. The fish can cultivate in a small water source like farm pond, burrow hole.

x. In our house we should keep ourselves keep safe from mosquito bite. Wearing long cloths, use net in the window and doors can be preventive measures.

xi. We can use mosquito repellent sprays, creams. Using coils or liquids to kill or drift away mosquitos. We should spray in dark places like behind calendar, photo frame and storeroom.

xii.   Using insecticidal spray can be a good solution. In our local areas is needed to kill mosquito. One problem is that people do not allow the spray workers in their house or surroundings. But they should be aware of the importance of the insecticide.

xiii.   TEMEPHOS which is an insecticide can be used to kill the larva. Another solution may be used which the combination of petrol or kerosene in water.

xiv.   It is mandatory to keep a dengue affected patient inside a mosquito net. Not only during the illness period but also after the recovery from the disease the patient should always stay under the net. (*Treatment, prevention and control global strategy for dengue prevention and control 2*, n.d.)-(Oliver, 2013).

Chapter 3

Methodology

A cross sectional study was carried out in the Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka. A special dengue cell or unit had been established for treating dengue patients. In that unit, only the dengue patients were allowed to stay. Dedicated physicians and nurses were available in the unit and the environment was quite satisfactory. Admitted patients stayed there until they recovery. They were always in the supervision of nurses and physicians come to see them frequently. Having discussion with the patients and their relatives, it has found that they were getting the best treatment from the unit.

A total of 60 patients of all ages were recruited for our survey. Among them some of the patients were in-patients and the rest of them were discharged by the hospital. We have collected 60 patients' profile and the prescriptions were analyzed. The prescriptions were compared with the national guideline and some other surveys. According to the core indicator of WHO the prescriptions were also analyzed.

3.1 Indicators examined:

   i.   Prescribing indicators

  ii.   Facility indicators

 iii.   Patient care indicators

 iv.   Complimentary indicators

3.2 Inclusion criteria:

   i.   All ages of patients were taken (From 0 to 70)

   ii.   Both male and female were included.

   iii. Diagnoses of being dengue positive.

3.3 Exclusion criteria:

   i.   Patients with concomitant infection.

   ii.   Monitoring the post conditions of discharged patients.

   iii. Patient suffered from normal fever.

3.4 Ethical aspects:

The study was approved by the authority of the Bangabandhu Sheikh Mujib Medical University (BSMMU). A legal permission was taken and all hospital criteria was maintained properly. All patients gave written consent to participate in this study.

3.5 Statistical analysis:

The collected data was analyzed statistically by using explanatory statistics and presented as percentages and counts. The result was delimitated in from if tables.

Chapter 4

Result

By analyzing the patients' profile, visiting hospital, monitoring patient care and counselling the following results have been found.

Table 1: Demographic profile

Patients criteria	Data
Total patients	60
Male: Female	41:19
Child	8
0-9 Years	7
10-19 Years	9
20-29 Years	9
30-39 Years	15
40-49 Years	6
50-59 Years	8
60-70 Years	6

Table 2: Prescribing indicators.

Prescribing indicators	Data
Average number of drugs per prescription	4-5
Percentage of drugs prescribed by generic name	15%
Percentage of encounters with an antibiotic prescribed	8%
Percentage of encounters with an injection prescribed	68%
Percentage of drugs prescribed from essential drugs list or formulary	50%

Table 3: Patient care indicators

Patient care indicators	Data
Average consultation time	4-5 minutes
Percentage of drugs actually dispensed in hospital attached pharmacy	100%
Percentage of drugs adequately labeled	100%
Average dispensing time	2-3 minutes

Patient's knowledge of correct dosage	50%

Table 4: Facility indicators

Facility indicators	Data
Availability of copy of essential drugs list	Yes
Availability of key drugs	Yes

Table 5: Complimentary indicators

Complimentary indicators	Data
Percentage of patients treated without drugs	0%
Average total drug cost per prescription	1050 Taka
Drug cost on injection per prescriptions	750 Taka
Drug cost on PPI per prescriptions	70 Taka / Week
Drug cost on Paracetamol per prescriptions	21 Taka / Week

4.1 Demographic profile

 In our pilot case study, the total number of patients was 60 and all 60 prescriptions were analyzed for the study. Among the 60 patients 41 patients were male and 19 were female. So, the number of male patients was double compared to females. However, if we focus on the age distribution of patients, there were 8 patients who were children. As they are very little, their immunology is weak than the adult ones. Their chance of dying is very significant and severe.

In Table 1 all the demographic data has been shown that from 0 to 9 ages there were 7 infected patients. So, children under age of 9 are at risk of dengue virus. From 10 to 19 years old there were 9 patients. That means, people including children and teenagers were also victim of dengue virus simultaneously. It was analyzed that around 9 people from 20 to 29 years old get affected who were mostly students and some of them were job holders. Additionally, the surprising number of affected people among 30 to 39 was 15. So, these groups of people were one-fourth among the affected people. In this age group most of the people were job holders and they were being affected very quickly. In the demographic profile table, the number of dengue affected people from 40 to 49 older age was 6. The number increases in the age group from 50 to 59. Around 8 patients were infected in that age group. Again, people aged between 60 to 70 was 6. So, people from every section of age group was getting affected by dengue virus. No age group got rid of dengue virus.

4.2 The prescribing indicators:

In order to determine the difference between the prescriptions, the prescribing indicators for the dengue affected people were calculated. They are mentioned bellow: -

i. Average number of drugs per prescriptions was 4 to 5. That means a patient had to take different types of drugs during his/her treatment period. Among them most common drugs were Paracetamol, PPI, anti-vomiting agent and saline. The medication varied according to the condition of the patients.

ii. Percentage of drugs prescribed in generic name was 15%. Rest 85% was prescribed in brand name. So, the patient had the less flexibility to choose brand by themselves. The pharmaceutical companies also influenced the physicians and the market economy also changes due to the brand name selection.

iii. Percentage of drugs prescribed with antibiotic was 8%. Though according to the national guideline of dengue treatment, there has forbidden the use of antibiotic. However, the reason of prescribing antibiotic may be the entity of another disease or the physician found it helpful while monitoring the patients.

iv. Percentage of patients treated with injection was 68%. It indicates the use of intravenous route. Saline was injected to patients. Some patients were unable to take ORS. For them it was necessary to inject saline.

v. Percentage of drugs prescribed from essential drugs list or formulary was 50%. Most commonly anti-pyretic, anti-emetics, antacids and multivitamin were prescribed.

4.3 Patient care indicators:

i. Average consultation time for a patient was found around 4 to 5 minutes. The time is not enough for a patient for better treatment. This happens because of a smaller number of physicians and the huge number of dengue patients. So, the patients are not getting enough

time from the physicians. So, in our country the patients are not getting enough time to consult with the doctors and they cannot share their problems and also not getting enough suggestions or advise which actually needed for them.

ii. The average dispensing time of drugs to the patients was 2 to 3 minutes. Actually, patients or their relatives who actually buy drugs are not getting enough time to visualize the drugs. The sellers in our country are not A grade pharmacist and that is why the patients and other people are not getting the facility.

iii. Percentage of drugs dispensed in hospital attached pharmacy was 100%. It is a good indication of a better treatment strategy. As all drugs were available, there was no trouble of finding any medicine.

iv. The percentage of drugs adequately labeled was 100%. It is very important for maintaining the quality and identity of the drugs.

v. Patient's knowledge of correct dosage was found 50%. As patients are taking the medication, they should know the dosage. It will help them for getting better knowledge about their medication.

4.4 Facility indicators:

i. There was the availability of copy of essential drugs list in the hospital pharmacy. It is needed for the safety, efficacy, cost effectiveness and satisfies the health care need of the people.

ii. There was also the availability of key drugs. The patients found all the drugs they needed for their treatment which indicate better treatment strategy.

4.5 Complimentary indicators:

i. Percentage of patients treated without drugs was 0%. So, there was no possibility of recovering from the disease without drugs. So, the virus is very serious and needs proper drugs in due time for relief.

ii. The average total drug cost per prescription was 1050 taka. In a developing country like Bangladesh, the cost is very high for a patient to bear. That also affects the economy of the country. Poor people suffer a lot for this.

iii. Drug cost on injection per prescriptions was 750 Taka. The amount was huge because it bears most of the cost of the prescription.

iv. Drug cost on PPI per prescriptions was 70 Taka per week. Proton pump inhibitor was used frequently.

v. Drug cost on Paracetamol per prescriptions was 21 taka per week. It indicates that acetaminophen was used for lowering the temperature and that cost was considerable.

4.6 Discussion

The survey helps us to perceive the number of patients exposed to the appointed drugs within a given period of time. The study consisted of people from different areas and backgrounds from all parts of Bangladesh. People from different places with different ages has been included to be analyzed by investigating their profile. In our study the number of female patients was half in compare to male patients. It may occur because of the lifestyle differences between male and female. As men are not so much careful about their health compared to the females. However, they travel a lot and visit different places which may be a reason of being affected by the virus. Hafeez

et all. mentioned that male was also infected more than female in their study. In their study the most common affected age group was in between 18-45. (Hafeez, 2011). In our study we have found the greatest number of patients (15 patients) belongs to the age group of 30-39. So, people from different age groups are infected by dengue in India and Bangladesh. Additionally, in the treatment or management of dengue fever intravenous fluid was the priority in some cases (Rajapakse et al.,2012)-(Rammohan, Bhandare, Adarsh, & Satyanarayana, 2018). In our study the same treatment strategy was followed by doctors by using more intravenous fluid to the patients. Antimicrobials were prescribed in so many cases of studies (Bhandare & Jeevangi, 2019)-(Management et al., 2011). In our survey use of antibiotic was also found. Reasons of using antibiotic may be treating another symptoms or physician found it helpful while treating patients though in the national guideline use of antibiotic is prohibited. In the study by Beg MA et all. antipyretics, antacid, antiemetic and multivitamin was prescribed frequently (Dutta, Beg, Bawa, Anjoom, & Vishal, 2015). Our patient's prescription also shows the use of these types of drugs but multivitamin was less frequently used. However, Papaya leaf was used in the treatment of many patients because it was supposed to increase platelet count (Bhandare & Jeevangi, 2019). We did not find any use of prescribing papaya leaf in our study. In our treatment system it can be used depending on the patient's acceptance and physician's observation. Another possible solution can be the use of rupatadine in our treatment strategy. Rupatadine is a second-generation antihistamine which is taken orally. It is normally used in histamine-1- receptor blocking process and also in PAF (Platelet-activating factor) receptor blocking activities to treat allergic reaction and choric urticaria. Rupatadine effects on reducing endothelial call permeability in vivo. It was also applied in mouse. Rupatadine helped in reducing vascular leak and increasing hematocrits count among the mouse (St John, Rathore, Raghavan, Ng, & Abraham, 2013). A study has done about the

efficacy of rupatadine over 67 patients in the treatment of dengue infection in Sri Lanka. There rupatadine was prescribed (10 mg and 40 mg) to the 67 patients. It was noticed that those patients recovered very quickly. 10mg of rupatadine was not enough to give optimum effect bur 40mg gave an outstanding positive effect. So, rupatadine contributed in controlling vascular leak and increased platelet count which were very much beneficial for the patients. Rupatadine was well tolerated by the patients and low in cost (Gathsaurie Neelika Malavige et al., 2018). As rupatadine was found effective and no harmful side effect was noticed, it can also be included in our treatment strategy. In our pilot case study, the consultation time for the patients was not enough. Patients need more time to consult with the physicians for better treatment. In our survey, it has found that all the drugs were adequately labeled and displayed in the hospital attached pharmacy which were positive side in our study. One drawback was found in drug dispensing time. The time was not adequate for the patients. Finally, the consultation time and drug dispensing time were not up to the mark at all and more focus should be given in these sectors.

4.7 Limitation

Due to the shortage of time and hospital protocols, only one hospital was involved in our survey. It would be better if two or more institutions could be engaged in our study. Another limitation was in the number of patients. In our study, only 60 patients' profile was applied. The number is not up to the mark. More data collection would obviously provide us better findings.

4.8 Recommendation

The study could be more selective. We could have taken same number of male and female patients and could analyze according to gender in prior to collection of data. The study could be further involved in the dengue virus attack for the posterior analysis in the future.

Chapter 5

Conclusion

Dengue virus infection is one of the significant health problems in Bangladesh. A lot of people especially children suffer from the attack. Mortality rate is also high and it crests negative impact on economy. The disease is communicable and for this prevention methods must be applied properly. Treatment strategy is improving day by day in our country and more focus should be given on new research and findings. Identifying dengue virus early can provide a patient better treatment and for this various diagnosis method need to be established and available. It would be better if vaccine can be invented accurately. Different age group should be aware of the epidemic conditions of the virus and keep themselves safe as far it is possible. Patients need more counselling, consulting time and need to follow up properly. So, proper awareness and with a great treatment strategy can protect people from dengue virus.

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